

REMARKS/ARGUMENTS

Claims 1-2, 4, and 5-25 are pending.

Claims 1, 6, 11, 13, 15-17, 20, and 22 have been amended.

Claims 3 and 5 have been cancelled.

Support for the amendments is found in the claims and specification (e.g., pages 1-2, paragraphs [0003]-[0005] and the Examples), as originally filed.

No new matter is believed to have been added.

Applicants wish to thank the Examiner for the discussion on February 4, 2010. The Applicants' representative explained the invention. The prior art rejections were discussed in view of the proposed amendments. The Examiner indicated that the rejections under 35 USC 112, would be likely withdrawn.

Claims 1, 4, 6-7, 13-18, and 22-25 are rejected under 35 U.S.C. 103(a) over Chen et al., US 2003/0211180 (Chen I), Ahmad et al., US 2006/0030578, and Messerer et al., Clin, Cancer Res., 10(19):6638-49 (October 1, 2004). The rejection is traversed because the combination of the references does not describe or suggest an injectable aqueous composition preparation comprising water, the claimed camptothecin, and acetic acid and sodium acetate, wherein camptothecin is solubilized in the aqueous solution of acetic acid and sodium acetate at a pH 2-5.

Chen I describes an oral composition or a suppository (claims 8-9) comprising a therapeutic agent. Chen I also describes a solution comprising irinotecan mixed with acetonitrile acidified with glacial acetic acid, wherein the solution is used in *in vitro* blood testing (i.e., externally) ([0265]-[0266]).

More specifically, pharmacokinetics of irinotecan was studied with relation to the herbal composition PHY906. [0265]. Irinotecan alone or in combination with PHY906 is administered, blood samples are collected, and the samples are processed with plasma added

to an internal standard solution consisting of 50  $\mu\text{g}/\text{ml}$  of camptothecin in acetonitrile acidified with glacial acetic acid (4 ml in 100 ml). [0266]. The internal standard solution is not injected but is used *externally* in for blood processing.

Ahmad et al. describe an oral lipid complex with irinotecan, wherein irinotecan is solubilized by *bonding* with a lipophilic compound or by *entrapping* within the interior of a liposome ([0050]). In the Ahmad et al. composition, irinotecan is not soluble in the aqueous solution of the acetic acid and sodium acetate at a pH of 2 to 5 but only in a lipid complex. An aqueous solution of irinotecan is prepared at a pH 7-11 ([0010] and [0013]). This solution is used for re-hydrating the lipid phase, and the pH of the lipid complex with irinotecan is then adjusted to a pH 1-3.5 ([0020], [0027]-[0020], and the Examples).

Ahmad et al. describe that irinotecan can be dissolved in an aqueous typical alkaline buffer (e.g., sodium acetate, [0010]). Ahmad et al. describe that after liposomes are rehydrated with an alkaline solution of SN38, the complex can be treated with an activating agent to activate SN38 in the complex with liposomes, wherein the activating agent is sodium citrate, acetic acid, etc. [0028].

Thus, in Ahmad et al., irinotecan is dissolved in sodium acetate (a typical alkaline buffer, [0010]), liposomes are rehydrated with the alkaline solution of SN38, and then the complex is treated with an activating agent (e.g., acetic acid) to activate SN38 in the complex with liposomes. Ahmad et al. do not describe solubilizing SN38 with acetic acid and sodium acetate an a pH 2-5 *without* forming a lipid complex with SN38.

The Examiner has admitted that Ahmad et al. teach liposomal irinotecan, see page 5, ln. 11-12 of the Official Action (OA).

The present specification describes that CPT-11 has low solubility in water and that encapsulating or incorporating in a polymer complex and heating have been tried to solubilize irinotecan. (See pages 1-3 of the specification). Also, in the Examples, a solution of

CPT-11, acetic acid, sodium acetate, and water (without using encapsulation or bonding with other agent, e.g., liposomes) is obtained and analyzed for solubility.

The Examiner has alleged that it would have been obvious to substitute glacial acetic acid for acetic acid in the composition of Chen I because sodium acetate and acetic acid are functional equivalents (i.e., acidic buffer agents) and one skilled in the art would have been motivated to substitute glacial acetic acid of Chen I with sodium acetate and expect the composition to have the same properties. Page 5, ln. 14-20, of the OA.

First, the Examiner is not clear whether glacial acetic acid is substituted for acetic acid, glacial acetic acid is substituted for sodium acetate, or glacial acetic acid is substituted for acetic acid and sodium acetate. In Chen I, glacial acetic acid is used for acidifying acetonitrile. However, as described in Ahmad et al., sodium acetate is a typical alkaline buffer, not an acidic buffering agent and, therefore, sodium acetate and acetic acid are not functional equivalents.

Second, the Examiner's conclusions are merely assertions because the Examiner has not provided any evidence supporting her allegations that sodium acetate and acetic acid are functional equivalents and upon substitution of glacial acetic acid in Chen I, the composition will have the same properties.

The rejection cannot be upheld because the Examiner's statements are merely unsupported allegations that are not based on objective evidence or acceptable scientific reasoning. The Federal Circuit has made it clear that obviousness rejections must be based on objective evidence of record. Cf. *In re Lee*, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) ("The factual inquiry whether to combine references must be thorough and searching.'...It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with."). For these reasons, the Examiner's rejection under 35 U.S.C. § 103(a) must be reversed.

Thus, the Examiner has not established a *prima facie* case of obviousness with respect to combining sodium acetate and acetic acid in the mixture of Chen I. The Office has the initial burden of proof to establish the *prima facie* obviousness of the subject matter Applicants claim in view of the prior art teaching. *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). Absent evidence which supports a rejection of the subject matter Applicants claim for obviousness, the Examiner's conclusion that Applicants' claims are unpatentable under 35 U.S.C. §103(a) must be withdrawn.

Further, the claimed preparation is injected, while the Ahmad et al. preparation is oral and compounds (e.g., chloroform, ethanol, etc.) which are not necessarily appropriate for injections, and in particular, intravenous injections. Also, the test sample of Chen I comprises acetonitrile and is used *in vitro*. Applicants submit Material Safety Data Sheets for acetonitrile, chloroform, and ethanol showing acute toxicity of these agents upon, e.g., oral administration, inhalation, skin and eye contact, etc. Thus, neither the composition of Ahmad et al. nor Chen I are injectable.

Moreover, although Messerer et al. describe administering liposomal irinotecan, the cited references do not describe or suggest an injectable aqueous composition preparation (e.g., intravenous) comprising water, camptothecin with acetic acid and sodium acetate which is solubilized at a pH 2-5. Also, the composition of Chen I which is modified based on the disclosure of Ahmad et al. is not liposomal. Thus, the Examiner is not clear as to what is modified, the composition of Chen I with the disclosure of Ahmad et al. or *vise versa*. It is not clear how the intravenous administration of Messerer et al.' *liposomal* irinotecan composition is relevant to administering the *aqueous* composition of Chen I and the claimed intravenous *aqueous* composition.

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Lastly, Messerer et al., *Clin, Cancer Res.*, 10(19):6638-49 (October 1, 2004), was published in October 2004, while the present application claims benefit of the filing date of JP 2004-035985 and JP 2004-035986, both filed on February 13, 2004. Thus, Messerer et al. is not a prior art reference.

Applicants filed a Request for priority under 35 U.S.C. 119 and the International Convention indicating that the certified copies of both priority documents were submitted to the International Bureau in PCT/JP05/01902 application. See the Request and the PCT Notification regarding submission of priority documents attached with this paper for the Examiner's convenience.

**Applicants request** granting benefit of the filing date of JP 2004-035985 and JP 2004-035986 and that the **Examiner acknowledges the claim for priority** made by Applicants.

Also, the cited references do not describe that the irinotecan composition comprises the component (C) as, e.g., in claims 2, 8-10, 14-15, 19-21, and 23.

Lastly, the combination of the references does not describe or suggest the claimed amounts of the components as, e.g., in claims 6-7, 11-13, 15-18, and 20-24.

Thus, Chen I, Ahmad et al., and Messerer et al. do not make the claimed composition obvious.

Applicants request that the rejection be withdrawn.

Claims 1, 4, 6-7, 13-18, and 22-25 are rejected under 35 U.S.C. 103(a) over Chen et al., US 2003/0211180 (Chen I), Ahmad et al., US 2006/0030578, Messerer et al., Clin, *Cancer Res.*, 10(19):6638-49 (2004), and Chen et al., US 6,383,471 (Chen II).

Claims 1, 4, 6-7, 13-18, and 22-25 are rejected under 35 U.S.C. 103(a) over Chen et al., US 2003/0211180 (Chen I), Ahmad et al., US 2006/0030578, Messerer et al., Clin,

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Cancer Res., 10(19):6638-49 (2004), and Remington's Pharmaceutical Sciences (pages 420-425, 1980) ("Remington's").

The rejections are traversed because the combinations of the references do not describe or suggest an injectable aqueous composition preparation comprising water, the claimed camptothecin, and acetic acid and sodium acetate, wherein camptothecin is solubilized in the aqueous solution of acetic acid and sodium acetate at a pH 2-5.

The disclosures of Chen I, Ahmad et al., and Messerer et al. are described above. Chen II or Remington's do not cure the deficiency.

Chen II describes an oral preparation of ionizable hydrophobic agents, wherein irinotican is one of the large number of possible agents (see col. 6-10). The Chen II formulations comprising the ionizable hydrophobic agents further comprise a carrier that includes a surfactant that is capable of solubilizing the hydrophobic agents, and an ionizing agent. Col. 4, ln. 29-41.

Although Chen II describes that an ionizing agent may be acetic acid or salt of acetic acid depending on the groups of ionizable hydrophobic agents to be ionized (col. 11, ln. 9-54), the Chen II ionizable hydrophobic agents are *solubilized* by using surfactants and additional solubilizers (col. 31-32), not by an ionizing agent.

Chen II does not describe that irinotican (one of the numerous hydrophobic agents) can be solubilized *without* using a surfactant and a solubilizer in an aqueous solution of acetic acid and sodium acetate.

In claim 1, acetic acid and sodium acetate solubilize 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin in the aqueous solution of the acetic acid and sodium acetate at a pH of 2 to 5, while in Chen II, hydrophobic agents are solubilised by a carrier that comprises a surfactant (col. 4, ln. 29-41; col. 13, ln. 61 to col. 14, ln. 2).

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Also, Remington's does not describe the elements missing in Chen I, Ahmad et al., and Messerer et al..

Thus, Chen I, Ahmad et al., Messerer et al., and Chen II or Remington's do not make the claimed solution preparation obvious.

Applicants request that the rejection be withdrawn.

Claims 1-2, 8, 11, 13, 15-17, 20, and 22 are rejected under 35 U.S.C. 112, second paragraph. Claims 1-2, 4, 6-8, and 11-25 are rejected under 35 U.S.C. 112, first paragraph.

The claims have been amended. It is believed that the claims are clear and supported in the original specification. Applicants request that the rejections be withdrawn.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

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<< No.07278 Chloroform >> P.1 / 7  
 Date of issue : 28 November, 2003  
 Date of revision : 1 July, 2009

## Material Safety Data Sheet

### 1. Product and company identification

Product name : Chloroform  
 Name of manufacturer : KANTO CHEMICAL CO., INC.  
 Address : 11-5 Nihonbashi Honcho 3-Chome, Chuo-Ku, Tokyo 103-0023 Japan  
 Name of section : Reagent division, catalog and products information section  
 Telephone number : +81-3-3639-8301  
 Facsimile number : +81-3-3639-9435  
 Mail address : BC32@gms.kanto.co.jp  
 MSDS No. : 07278  
 Product numbers applied by the MSDS : 07278, 08097, 08277

### 2. Summary of danger and Hazard

#### GHS classification

##### Physical and chemical hazard

Flammable liquids : Out of category  
 Pyrophoric liquids : Out of category  
 Self-heating substances and mixtures : Out of category  
 Corrosive to metals : Out of category

##### Human health hazard

Acute toxicity(oral) : Category 4

Skin corrosion · Irritation : Category 1A

Serious eye damage · Eye irritation : Category 1

##### Germ cell mutagenicity

: Category 2

Carcinogenicity : Category 2

##### Reproductive toxicity

: Category 2

##### Specific target organ systemic toxicity(single exposure)

: Category 1 . Category 3 (anesthetic action)

##### Specific target organ systemic toxicity(repeated exposure)

: Category 1

##### Environmental hazard

###### Hazardous to the aquatic environment-acute hazard

: Category 2

###### Hazardous to the aquatic environment-chronic hazard

: Category 2



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## Pictogram or symbol



## Signal word

: Danger

## Hazard statement

: Harmful if swallowed

Causes severe skin burns and eye damage

Causes serious eye damage

Suspected of causing genetic defects

Suspected of causing cancer

Suspected of damaging fertility or the unborn child

Causes damage to organs (liver, kidneys)

May cause drowsiness and dizziness

Causes damage to organs (central nervous system, kidneys, liver, respiratory organs) through prolonged or repeated exposure

Toxic to aquatic life

Toxic to aquatic life with long lasting effects

## Cautions

## Safety measurements

: Do not handle until all safety precautions have been read and understood.

Do not breathe dust, mist, and vapor.

Use only in a well-ventilated area.

Avoid release to the environment.

Do not eat, drink or smoke when using this product.

Wear appropriate protective gloves, glasses, clothing, face shield, or mask.

Wash protective equipment thoroughly after use.

Wash hands thoroughly after handling.

## First-aid measures

: If inhaled : Remove victim to fresh air and keep at rest in a position comfortable for breathing. Get medical treatment if you feel unwell.

If swallowed: Rinse mouth, do not induce vomiting. Immediately get medical treatment.

If in eyes : Rinse cautiously with water for several minutes. Get medical treatment.

If on skin : Remove contaminated clothing and the substance. Immediately get medical treatment.

If exposed, get medical treatment.

Get medical treatment, if you feel unwell.

Collect leakage

## Storage

: Tightly container closed and store in a well-ventilated area.

Store locked up.

## Disposal

: Dispose of contents and containers appropriately in accordance with related regulations.

## 3. Composition/Information on ingredients

Substance/Mixture : Substance

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## Chemical name or commercial name

: Chloroform

## Ingredients and composition

: Chloroform min. 99.0%

## Chemical formula

: CHCl<sub>3</sub>

## CAS No.

: 67-66-3

## TSCA Inventory

: Registered

## EINECS No.

: 2006638

## Dangerous and hazardous ingredients

: Chloroform

## 4. First aid measures

Inhalation : Remove the victim to fresh air, and make him blow his nose and gargle.

Skin contact : Wash the affected areas under running water.

Eye contact : Wash the affected areas under running water for at least 15 minutes.  
 Get medical treatment.

Ingestion : Do not induce vomiting because the chemical has high volatility and  
 may increase the risk of aspiration of it into the lungs. Get medical  
 treatment.

## Anticipated acute and delayed symptoms

: Inhalation may causes cough, dizziness, lethargy, sensory paralysis,  
 headache, nausea, vomiting, unconsciousness these symptoms may be  
 late to develop. these symptoms may be late to develop.

## Protection for first aid person

: Savers wear proper protective equipment like rubber gloves, goggles.

## 5. Fire fighting measures

Extinguishing media : Dry chemical powder, carbon dioxide, dry sand, foam

## Prohibited extinguishing media

: Water spray

## Danger and hazards under fire

: Thermal decomposition emits harmful chlorine, hydrogen chloride,  
 phosgene gas.

Particular fire fighting : Move containers from fire area if it can be done without risk, if not  
 possible, apply water from a safe distance to cool and protect  
 surrounding area.

Keep personnel removed from and unwind of fire.

Dry chemical powder, carbon dioxide or dry sand should be used for  
 small fires. Foam extinguisher is effective for a large scale fire.

## Protection for firefighters

: Firefighters should wear protective equipment.

## 6. Accidental release measures



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**Cautions for personnel** : Wear proper equipment and avoid contact with skin and inhalation of vapor. Keep personnel removed from and upwind of fire. Shut off all sources of ignition. Keep away personnel except for authorized ones from spillage area by stretching ropes.

**Cautions for environment** : Attention should be given not to cause damage to the environment by flowing of spillage to rivers.

**Removal measure** : Absorb spill with inert material (e.g., diatomaceous earth, sand) and flush residual area with copious amounts of water.

## 7. Cautions of handling and storage

### Handling

**Engineering measures** : Wear proper protective equipment not to contact with skin or inhale the vapor.

### Cautions for safety handling

: Use with an enclosed system or a local exhaust ventilation.

### Storage

#### Adequate storage condition

: Store in a dark, cool place and tightly closed.

#### Safety adequate container materials

: Glass, fluorine resin

Do not use vinyl chloride resin, polyethylene, synthetic rubber etc.

## 8. Exposure control/Personal protection

**Engineering measures** : Use only with adequate ventilation and in closed systems.

### Control parameters

ACGIH(2007) : 10ppm(TLV-TWA)

### Protective equipment

#### Respiration protective equipment

: Chemical cartridge respirator with an organic vapor cartridge or airline respirator

#### Hands protective equipment

: Solvent resistance protective gloves (Neoprene), Nitryl rubber or polyvinyl chloride protective gloves are not suitable.

#### Eyes protective equipment

: Safety goggles

#### Skin and body protective equipment

: Protective clothing, protective boots

## 9. Physical and chemical properties

**Appearance** : Liquid

**Color** : Colorless

**Odor** : Sweet acrid odor

**Odor threshold** : 30ppm

**Boiling point** : 61.15°C

**Melting point** : -63.55°C

**Flash point** : Noncombustible

**Vapor pressure** : 212hPa(20°C)

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Vapor density : 4.1  
 Specific gravity : 1.489g/ml (20°C)  
 Solubility  
   Solubility in solvents : Water ; 0.8g/water 100ml (20°C)  
     Organic solvents ; Readily soluble in ethanol, diethyl ether.  
 log Pow : 1.97  
 Other data : Viscosity : 0.563cP(20°C)

#### 10. Stability and reactivity

Stability : Decomposes by light or heat and emits harmful phosgene.  
 Reactivity : If contacted with strong alkaline solution, may cause explode.  
 Incompatible conditions : Light, heat  
 Incompatible materials : Oxidizing substances  
 Hazardous decomposition products : Carbon monoxide, Chlorine, Hydrogen chloride, Phosgene

#### 11. Toxicological information

Acute toxicity : Harmful if swallowed(category 4)  
   Dermal : Not possible to classify because of insufficient data.  
   Inhalation(vapor) : Not possible to classify because of insufficient data.  
   Inhalation(dust, mist) : Not possible to classify because of insufficient data.  
   rat oral LD50=635mg/kg (as calculated value)  
   mouse oral LD50=1120mg/kg  
   rat inhalation LC50=75g/m3/60M  
   mouse inhalation LCL0=23g/m3/56M  
   human inhalation LCL0=25000ppm/5M

Skin corrosiveness : Causes severe skin burns and eye damage(category 1A)  
   Based on the evidence of slight congestion in the skin, moderate skin necrosis and incrustation from the rabbit skin irritation test.

Irritation to skin, eyes : Causes serious eye damage(category 1)  
   Based on the evidence of severe eye irritation, with mydriasis and keratitis in all rabbits. Translucent zones in the cornea were observed in four animals and a purulent hemorrhagic discharge was also reported (number of rabbits unknown).

Respiratory sensitization or Skin sensitization : Respiratory sensitization : Not possible to classify because of insufficient data.  
   Skin sensitization : Not possible to classify because of insufficient data.

Mutagenicity : Suspected of causing genetic defects(category 2)  
   Based on positive data on somatic cell mutagenicity tests in vivo (micronucleus and chromosome aberration tests).

Carcinogenic effects : Suspected of causing cancer(category 2)

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Japan Society for Occupational Health classifies the chemical as the group 2B. (The chemical is possibly carcinogenic to humans.)

#### Effects on the reproductive system

- : Suspected of damaging fertility or the unborn child(category 2)  
 Based on the evidence of a decline in fertility, a decrease in crown-rump length, delayed calcification of the skull and lumbar ribs, an increase in cleft palate, malformation of the interperietal bone, increased incidence of anuria, brachyury and anal atresia within a litter, subcutaneous edema and increased rates of absorbed embryos at dosing levels toxic to parent animals in mouse three-generation tests and rat and mouse teratogenicity tests.

#### Specific target organ systemic toxicity single exposure

- : Cause damage to organs (liver, kidneys) (category 1)  
 May cause drowsiness and dizziness (category 3)  
 Based on the human evidence including necrosis of hepatic cells, liver damage, jaundice, hypertrophy of the liver, kidney damage, stertorous respiration, cyanosis and excessive sweating and the evidence from animal studies including centrilobular fatty infiltration and necrosis of the liver, piloerection, sedation, muscular relaxation, ataxia, debility, partially watery eyes and necrosis of proximal convoluted tubules.

#### Specific target organ systemic toxicity repeated exposure

- : Cause damage to organs (central nervous system, kidneys, liver, respiratory organs) through prolonged or repeated exposure (category 1)  
 Based on the human evidence including fatigue, thirst, gastrointestinal pain, frequent and painful urination, difficulty in concentration, depression, irritability, jaundice caused by liver damage after exposure to chloroform.

#### Aspiration hazard

- : Not possible to classify because of insufficient data.

### 12. Ecological information

#### Ecotoxicity

- |               |   |
|---------------|---|
| Fish toxicity | : Toxic to aquatic life (category 2)<br>Toxic to aquatic life with long lasting effects (category 2)<br>Fish (rainbow trout) LC50=1.24-2.03mg/l/96H |
|---------------|---|

#### Residuality and degradability

- : Non biodegradability  
 0% by BOD

- |               |   |
|---------------|---|
| Ecoreiduality | : Low or non bioaccumulative or residuality in fish or shells.<br>Concentration Carp 1.4-4.7 fold(1mg/l)<br>Carp 4.1-13 fold(0.1mg/l) |
|---------------|---|

- |          |  |
|----------|--|
| Mobility | : May transfer to the atmosphere, water or soil because of physical and chemical properties. |
|----------|--|

### 13. Disposal consideration

- |                   |  |
|-------------------|--|
| Residual disposal | : Mix the material with combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber as possible as high temperature. Or else consult approved disposal companies. |
| <Note>            | : Alkaline solution should be used for cleaning liquid of the scrubber.  |

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The incinerator should be suitable for burning organic halide compounds.

**Containers** : In case of disposal of empty bottles, dispose bottles after removing the content thoroughly.

#### 14. Transport information

UN class : Class 6.1(Toxic substances) P. G. III

UN number : 1888

#### Marine regulation information

UN No. : 1888

Proper shipping name : CHLOROFORM

Class : 6.1

Sub risk : -

Packing group : III

Marine pollutant : Not applicable

#### Aviation regulation information

UN No. : 1888

Proper shipping name : Chloroform

Class : 6.1

Sub risk : -

Packing group : III

#### 15. Regulatory information

Ensure this material in compliance with federal requirements and ensure conformity to local regulations.

#### 16. Other information

##### References

Solvents Handbook, T. Asahara et, Kodansha Scientific Ltd. (1976)

Registry of Toxic Effects of Chemical Substances (RTECS) 1985-86 ed.  
 National Instituted for Occupational Safety and Health(1987)

Handbook of 15509 Chemical Products, The Chemical Daily Co. (2009)

The information contained herein is based on several references and the present state of our knowledge. However the MSDS does not always cover all information about the product, handle the product carefully. The information is intended to ordinary usage, in case of particular handlings, conduct appropriate safety measurements. The information herein is only provision of information, and it does not represent a guarantee the properties of the product.



Kanto Chemical Co., Inc.

<< No.01031 Acetonitrile >> P.1 / 7  
 Date of issue : 18 September, 2003  
 Date of revision : 21 January, 2010

## Material Safety Data Sheet

### 1. Product and company identification

Product name : Acetonitrile  
 Name of manufacturer : KANTO CHEMICAL CO., INC.  
 Address : 11-5 Nihonbashi Honcho 3-Chome, Chuo-Ku, Tokyo 103-0023 Japan  
 Name of section : Reagent division, catalog and products information section  
 Telephone number : +81-3-3639-8301  
 Facsimile number : +81-3-3639-9435  
 Mail address : BC32@gms.kanto.co.jp  
 MSDS No. : 01031  
 Product numbers applied by the MSDS : 01031, 01030, 01033, 01837, 01952

### 2. Summary of danger and Hazard

#### GHS classification

##### Physical and chemical hazard

Flammable liquids : Category 2  
 Pyrophoric liquids : Out of category  
 Corrosive to metals : Out of category

##### Human health hazard

Acute toxicity(oral) : Category 5

Acute toxicity(dermal) : Category 3

Acute toxicity(inhalation:vapors) : Out of category

##### Skin corrosion · Irritation

: Out of category

##### Serious eye damage · Eye irritation

: Category 2A

##### Germ cell mutagenicity

: Category 2

##### Carcinogenicity

: Out of category

##### Specific target organ systemic toxicity(single exposure)

: Category 1

##### Specific target organ systemic toxicity(repeated exposure)

: Category 2

#### Environmental hazard

##### Hazardous to the aquatic environment-acute hazard

: Out of category

##### Hazardous to the aquatic environment-chronic hazard

: Out of category



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Date of issue : 18 September, 2003

Date of revision : 21 January, 2010

**Pictogram or symbol****Signal word**

: Danger

**Hazard statement**

: Highly flammable liquid and vapor  
 May be harmful if swallowed  
 Toxic in contact with skin  
 Causes serious eye irritation  
 Suspected of causing genetic defects  
 Causes damage to organs (central nervous system, respiratory organs)  
 May cause damage to organs (central nervous system, respiratory organs, kidneys, blood system, liver) through prolonged or repeated exposure

**Cautions****Safety measurements**

: Do not handle until all safety precautions have been read and understood.  
 Keep away from ignition sources such as heat, sparks, or open flame.  
 Keep containers tightly closed.  
 Ground container and receiving equipment in case of transport and stirring.  
 Use explosion-proof apparatus.  
 Use only non-sparking tools.  
 Do not breathe dust, mist, and vapor.  
 Do not eat, drink or smoke when using this product.  
 Wear appropriate protective gloves, glasses, clothing, face shield, or mask.  
 Wash hands thoroughly after handling.

**First-aid measures**

: If swallowed: Rinse mouth. Get medical treatment if you feel unwell.  
 If in eyes : Rinse cautiously with water for several minutes. Get medical treatment.  
 If on skin : Remove contaminated clothing and the substance. Get medical treatment, if you feel unwell.  
 Wash hands thoroughly after handling.  
 If exposed, get medical treatment.

Get medical treatment, if you feel unwell.

**Storage**

: Store in a cool and well-ventilated area.  
 Store locked up.

**Disposal**

: Dispose of contents and containers appropriately in accordance with related regulations.

**3. Composition/Information on ingredients**

Substance/Mixture : Substance

Chemical name or commercial name

: Acetonitrile

Ingredients and composition

: Acetonitrile min. 99.0%

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Date of issue : 18 September, 2003

Date of revision : 21 January, 2010

Chemical formula : CH<sub>3</sub>CN  
 CAS No. : 75-05-8  
 TSCA Inventory : Registered  
 EINECS No. : 2008352  
 Dangerous and hazardous ingredients  
                   : Acetonitrile

**4. First aid measures**

Inhalation : Remove the victim to fresh air, and make him blow his nose and gargle.  
 Skin contact : Wash the affected areas under running water.  
 Eye contact : Wash the affected areas under running water for at least 15 minutes.  
                If necessary, get medical treatment.  
 Ingestion : Give the victim water or salt water and make him vomit. Get medical attention.  
 Protection for first aid person  
                   : Savers wear proper protective equipment like rubber gloves, goggles.

**5. Fire fighting measures**

Extinguishing media : Water, dry chemical powder, carbon dioxide, dry sand  
 Prohibited extinguishing media  
                   : None  
 Particular fire fighting : Move containers from fire area if it can be done without risk, if not possible, apply water from a safe distance to cool and protect surrounding area.  
                           Dry chemical powder, carbon dioxide or dry sand should be used for small fires. Foam extinguisher is effective for a large scale fire.  
 Protection for firefighters  
                   : Wear breathing apparatus.

**6. Accidental release measures**

Cautions for personnel : Wear proper equipment and avoid contact with skin and inhalation of vapor. Keep personnel removed from and upwind of fire. Shut off all sources of ignition. Keep away personnel except for authorized ones from spillage area by stretching ropes.  
 Cautions for environment : Attention should be given not to cause damage to the environment by flowing of spillage to rivers. In case of the dilution of copious water, do not cause damage to the environment by untreated wastewater.  
 Removal measure : Absorb spill with inert material (e.g., diatomaceous earth, sand) and flush residual area with copious amounts of water.  
 Prevention of second accident  
                   : Remove nearby sources of ignition and prepare extinguishing media.

**7. Cautions of handling and storage**

Handling  
 Engineering measures : Wear proper equipment not to contact with skin or inhale the vapor.  
                           Fire is strictly prohibited.  
                           Ventilate well at working places.  
 Cautions for safety handling

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- Cautions** : Use with an enclosed system or a local exhaust ventilation.  
 : Do not contact with oxidizing substances.
- Storage**
- Adequate storage condition** : Store in a dark, cool place and tightly closed.
- Safety adequate container materials**
- : Glass, fluorine resin  
 Do not use polyvinyl chloride resin, polystyrene, polycarbonate.
- 8. Exposure control/Personal protection**
- Engineering measures** : Use only with adequate ventilation and in closed systems.
- Control parameters**
- ACGIH(2009) : 20ppm(TLV-TWA)  
 Transdermal absorption
- Protective equipment**
- Respiration protective equipment** : Chemical cartridge respirator with an organic vapor cartridge or airline respirator
- Hands protective equipment** : Impervious protective gloves
- Eyes protective equipment** : Safety goggles
- Skin and body protective equipment** : Protective clothing, protective boots

**9. Physical and chemical properties**

- Appearance** : Liquid
- Color** : Colorless
- Odor** : Ether like odor
- Boiling point** : 81.6°C
- Melting point** : -43.8°C
- Flash point** : 5.6°C
- Auto-ignition point** : 525°C
- Explosion characteristics**
- Explosion limit** : upper : 16vol% lower : 4.4vol%
- Vapor pressure** : 97hPa(20°C)
- Vapor density** : 1.4
- Specific gravity** : 0.782g/ml(20°C)
- Solubility**
- Solubility in solvents** : Water ; Freely soluble  
 Organic solvents ; Freely soluble in ethanol, diethyl ether, etc.
- log Pow** : -0.34
- Other data** : Viscosity : 0.375cP(15°C)

**10. Stability and reactivity**

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Stability : Stable under normal usage.  
 Reactivity : May react with oxidizing substances.  
 Incompatible conditions : Light, heat  
 Incompatible materials : Oxidizing substances  
 Hazardous decomposition products : Carbon monoxide, nitrogen oxides

**11. Toxicological information**

Acute toxicity : May be harmful if swallowed(category 5)  
 Toxic in contact with skin(category 3)  
 Inhalation(vapor) : Out of category  
 Inhalation(dust, mist) : Not possible to classify because of insufficient data.  
 rat oral LD50=2080mg/kg (as calculated value)  
 rabbit inhalation LC50=16000ppm/4H  
 rat skin LD50=390mg/kg

Skin corrosiveness : Out of category  
 Draize scores are all "0" for all subjects throughout the observation period: no skin irritation is observed.

Irritation to skin, eyes : Causes serious eye irritation(category 2A)  
 According to the rabbit eye irritation tests, the average scores of corneal opacity and conjunctival injection stand at 1.45 and 3, respectively.

Respiratory sensitization or Skin sensitization : Respiratory sensitization : Not possible to classify because of insufficient data.  
 Skin sensitization : Not possible to classify because of insufficient data.

Mutagenicity : Suspected of causing genetic defects(category 2)  
 Positive at body cell in vivo mutagenicity test (small nuclei test)

Carcinogenic effects : Out of category  
 ACGIH classifies the group A4(not classifiable as a human carcinogen).

**Effects on the reproductive system**

: Not possible to classify because of insufficient data.

**Specific target organ systemic toxicity single exposure**

: Cause damage to organs (central nervous system, respiratory organs) (category 1)  
 Based on the human evidence including pectoralgia, tightness of the chest, nausea, vomiting, tachycardia, hypotension, tachypnea, headache, insomnia, clouding of consciousness, spasm.

**Specific target organ systemic toxicity repeated exposure**

: May cause damage to organs (central nervous system, respiratory organs, kidneys, blood system, liver) through prolonged or repeated exposure(category 2)

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Based on the evidence from animal studies including "hyperextensive reflex, excitement, asynergia, chronic pneumonia, pulmonary emphysema, atelectasis, pleural effusion, coagulation of alveolar histiocytes, cellular infiltration of alveolar septa, bronchitis, localized cloudy swelling of proximal convoluted renal tubules and convoluted renal tubules, localized extradural/subdural hemorrhage".

Aspiration hazard : Not possible to classify because of insufficient data.

#### 12. Ecological information

##### Ecotoxicity

Fish toxicity : Acute aquatic toxicity : Out of category  
 Chronic aquatic toxicity : Out of category  
 Red killifish LC50>100mg/l/96H

##### Rediualbility and degradability

: High biodegradability

Ecorediualbility : Not available

#### 13. Disposal consideration

Residual disposal : Burn in a chemical incinerator equipped with an afterburner and a scrubber. Or entrust approved waste disposal companies with the disposal.

Containers : In case of disposal of empty bottles, dispose bottles after removing the content thoroughly.

#### 14. Transport information

UN class : Class 3(Flammable liquids) P. G. II

UN number : 1648

##### Marine regulation information

UN No. : 1648

Proper shipping name : ACETONITRILE

Class : 3

Sub risk : -

Packing group : II

Marine pollutant : Not applicable

##### Aviation regulation information

UN No. : 1648

Proper shipping name : Acetonitrile

Class : 3

Sub risk : -

Packing group : II

#### 15. Regulatory information

Ensure this material in compliance with federal requirements and ensure conformity to local regulations.

#### 16. Other information

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Date of issue : 18 September, 2003

Date of revision : 21 January, 2010

## References

- Dictionary of Organic Compounds, The society of Synthetic Organic Chemistry, Kodansha Ltd. (1985)  
Dangerous Properties of Industrial Materials, 6th ed. N. I. Sax Van Nostrand Reinhold Company (1984)  
Handbook of 15509 Chemical Products, The Chemical Daily Co. (2009)  
Handbook of Poisonous and Deleterious substances, revised and enlarged edition, Yakumu Kohosa (2000)

The information contained herein is based on several references and the present state of our knowledge. However the MSDS does not always cover all information about the product, handle the product carefully. The information is intended to ordinary usage, in case of particular handlings, conduct appropriate safety measurements. The information herein is only provision of information, and it does not represent a guarantee the properties of the product.

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Date of revision : 2 December, 2009

## Material Safety Data Sheet

### 1. Product and company identification

Product name : Ethanol  
 Name of manufacturer : KANTO CHEMICAL CO., INC.  
 Address : 11-5 Nihonbashi Honcho 3-Chome, Chuo-Ku, Tokyo 103-0023 Japan  
 Name of section : Reagent division, catalog and products information section  
 Telephone number : +81-3-3639-8301  
 Facsimile number : +81-3-3639-9435  
 Mail address : BC32@gms.kanto.co.jp  
 MSDS No. : 14033  
 Product numbers applied by the MSDS : 14033, 14039, 14599, 14649

### 2. Summary of danger and Hazard

#### GHS classification

##### Physical and chemical hazard

Flammable liquids : Category 2  
 Pyrophoric liquids : Out of category  
 Self-heating substances and mixtures : Out of category  
 Corrosive to metals : Out of category

##### Human health hazard

Acute toxicity(oral) : Out of category  
 Acute toxicity(inhalation:vapors) : Out of category  
 Acute toxicity(inhalation:dust, mists) : Out of category

Skin corrosion · Irritation : Out of category  
 Serious eye damage · Eye irritation : Category 2A

##### Germ cell mutagenicity

: Category 1B

Carcinogenicity : Out of category

##### Reproductive toxicity

: Category 1A

Specific target organ systemic toxicity(single exposure)

: Category 3 (respiratory tract irritation) , Category 3 (anesthetic action)

Specific target organ systemic toxicity(repeated exposure)

: Category 1 , Category 2



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**Environmental hazard**

Hazardous to the aquatic environment-acute hazard

: Out of category

Hazardous to the aquatic environment-chronic hazard

: Out of category

**Pictogram or symbol****Signal word**

: Danger

**Hazard statement**

: Highly flammable liquid and vapor

Causes serious eye irritation

May cause genetic defects

May damage fertility or the unborn child

May cause respiratory irritation

May cause drowsiness and dizziness

Causes damage to organs (liver) through prolonged or repeated exposure

May cause damage to organs (nervous system) through prolonged or repeated exposure

**Cautions****Safety measurements**

- : Do not handle until all safety precautions have been read and understood.
- Keep away from ignition sources such as heat, sparks, or open flame.
- Keep containers tightly closed.
- Ground container and receiving equipment in case of transport and stirring.
- Use explosion-proof apparatus.
- Use only non-sparking tools.
- Do not breathe dust, mist, and vapor.
- Use only in a well-ventilated area.
- Do not eat, drink or smoke when using this product.
- Wear appropriate protective gloves, glasses, clothing, face shield, or mask.
- Wash hands thoroughly after handling.

**First-aid measures**

- : If inhaled : Remove victim to fresh air and keep at rest in a position comfortable for breathing. Get medical treatment if you feel unwell.

If in eyes : Rinse cautiously with water for several minutes. Get medical treatment.

If on skin : Remove contaminated clothing and the substance. Get medical treatment, if you feel unwell.

Wash hands thoroughly after handling.

If exposed or concerned, get medical treatment.

Get medical treatment, if you feel unwell.

**Storage**

- : Tightly container closed and store in a well-ventilated area.
- Store locked up.

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**Disposal** : Dispose of contents and containers appropriately in accordance with related regulations.

### 3. Composition/Information on ingredients

Substance/Mixture : Substance

Chemical name or commercial name

: Ethanol

Ingredients and composition

: Ethanol min. 99.5%

Chemical formula : C<sub>2</sub>H<sub>5</sub>OH

CAS No. : 64-17-5

TSCA Inventory : Registered

EINECS No. : 2005786

Dangerous and hazardous ingredients

: Ethanol

### 4. First aid measures

Inhalation : Remove the victim to fresh air, and make him blow his nose and gargle.

Skin contact : Wash the affected areas under running water.

Eye contact : Wash the affected areas under running water for at least 15 minutes. If necessary, get medical treatment.

Ingestion : Give the victim one or two glasses of water or sodium chloride water solution and induce vomiting. Do not give an unconscious victim anything to drink. Get medical treatment.

Anticipated acute and delayed symptoms

: Inhalation causes cough, headache, feeling of fatigue, and lethargy.

Protection for first aid person

: Savers wear proper protective equipment like rubber gloves, goggles.

### 5. Fire fighting measures

Extinguishing media : Water, dry chemical powder, carbon dioxide, dry sand

Prohibited extinguishing media

: Foam extinguisher

Particular fire fighting : Move containers from fire area if it can be done without risk, if not possible, apply water from a safe distance to cool and protect surrounding area.

Dry chemical powder, carbon dioxide or dry sand should be used for small fires. Alcohol-resistant foam extinguisher is effective for a large scale fire.

Protection for firefighters

: Wear breathing apparatus.

### 6. Accidental release measures



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- Cautions for personnel** : Wear proper equipment and avoid contact with skin and inhalation of vapor. Keep personnel removed from and upwind of fire. Shut off all sources of ignition. Keep away personnel except for authorized ones from spillage area by stretching ropes.
- Cautions for environment** : Attention should be given not to cause damage to the environment by flowing of spillage to rivers. In case of the dilution of copious water, do not cause damage to the environment by untreated wastewater.
- Removal measure** : Absorb spill with inert material (e.g., diatomaceous earth, sand) and flush residual area with copious amounts of water.
- Prevention of second accident** : Remove nearby sources of ignition and prepare extinguishing media.

## 7. Cautions of handling and storage

### Handling

- Engineering measures** : Wear proper equipment not to contact with skin or inhale the vapor. Fire is strictly prohibited.  
Ventilate well at working places.  
Prevent build-up of electrostatic charges (e.g. by grounding).

### Cautions for safety handling

- : Use with an enclosed system or a local exhaust ventilation.  
**Cautions** : Do not contact with oxidizing substances.

### Storage

#### Adequate storage condition

- : Store in a dark, cool place and tightly closed.

#### Safety adequate container materials

- : Glass, fluorine resin, stainless steel  
Do not use polyvinyl chloride resin, acrylic resin.

## 8. Exposure control/Personal protection

- Engineering measures** : Use only with adequate ventilation and in closed systems.

### Control parameters

- ACGIH(2009) : 1000ppm (TLV-STEL)

### Protective equipment

#### Respiration protective equipment

- : Chemical cartridge respirator with an organic vapor cartage or airline respirator

#### Hands protective equipment

- : Impervious protective gloves

#### Eyes protective equipment

- : Safety goggles

#### Skin and body protective equipment

- : Protective clothing, protective boots

## 9. Physical and chemical properties

- Appearance** : Liquid

- Color** : Colorless

- Odor** : Aromatic odor

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Boiling point : 78.3°C

Melting point : -114.1°C

Flash point : 14°C

Auto-ignition point : 363°C

**Explosion characteristics**

Explosion limit : upper : 19.0vol% lower : 4.3vol%

Vapor pressure : 59hPa(20°C)

Vapor density : 1.59

Specific gravity : 0.79g/ml(20°C)

**Solubility**

Solubility in solvents : Water : Freely soluble

Organic solvents : Miscible with many kinds of organic solvents like diethyl ether, chloroform.

log Pow : -0.32

Other data : Viscosity : 1.17cP(20°C)

**10. Stability and reactivity**

Stability : Stable under normal usage.

Reactivity : May react with strong oxidizing substances.

Incompatible conditions : Light, heat

Incompatible materials : Oxidizing substances

Hazardous decomposition products  
: Carbon monoxide**11. Toxicological information**

Acute toxicity : Oral : Out of category

Dermal : Not possible to classify because of insufficient data.

Inhalation(vapor) : Out of category

Inhalation(dust, mist) : Out of category

rat oral LD50=14g/kg

dog oral LD50=5500mg/kg

rat inhalation LC50=31600ppm/4H(as vapor)

rat inhalation LC50=63000ppm/4H(as mist)

Skin corrosiveness : Out of category

There is a mention that ethanol has no irritation by test of OECD TG404 and American guidelines.

Irritation to skin, eyes : Causes serious eye irritation(category 2A)

There is a mention that ethanol is classified as moderate by test of OECD TG404 and Draize method, and damage of cornea epithelia and conjunctive congestion can recover for one or two days.

Respiratory sensitization or Skin sensitization

: Respiratory sensitization : Not possible to classify because of insufficient data.



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**Skin sensitization** : Not possible to classify because of insufficient data.

**Mutagenicity**

: May cause genetic defects (category 1B)

There is a mention that ethanol has dominant lethality of rats and mice, aneuploidy induction on mice reproductive cells.

**Carcinogenic effects**

: Out of category

ACGIH classifies the group A4(not classifiable as a human carcinogen).

**Effects on the reproductive system**

: May damage fertility or the unborn child (category 1A)

Many harmful influence are reported that a large dose regular intake of alcohol causes malformed human embryo.

**Specific target organ systemic toxicity single exposure**

: May cause respiratory irritation (category 3) • May cause drowsiness and dizziness (category 3)

Oral intake of ethanol by human causes the damage of central nerve system, headache, fatigue, and loss of concentration. In case of acute toxicity, may dye.

**Specific target organ systemic toxicity repeated exposure**

: Cause damage to organs (liver) through prolonged or repeated exposure (category 1)

May cause damage to organs (nervous system) through prolonged or repeated exposure (category 2)

A large dose prolong intake of alcohol by human causes damages of most organs, but harm the liver the most. The liver turns to hepatitis steatosis at beginning, and hepatitis cirrhosis through necrosis and fibrosis.

**Aspiration hazard**

: Not possible to classify because of insufficient data.

**12. Ecological information****Ecotoxicity****Fish toxicity**

: Acute aquatic toxicity : Out of category

Chronic aquatic toxicity : Out of category

Daphnia magna LC50=5463.9mg/l/48H

**Rediduality and degradability**

: High biodegradability

**13. Disposal consideration****Residual disposal**

: Burn in a chemical incinerator equipped with an afterburner and a scrubber. Or entrust approved waste disposal companies with the disposal.

**Containers**

: In case of disposal of empty bottles, dispose bottles after removing the content thoroughly.

**14. Transport information**

**UN class** : Class 3(Flammable liquids) P. G. II

**UN number** : 1170

**Marine regulation information**

**UN No.** : 1170

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Proper shipping name : ETHANOL  
 Class : 3  
 Sub risk : -  
 Packing group : II  
 Marine pollutant : Not applicable

**Aviation regulation information**

UN No. : 1170  
 Proper shipping name : Ethanol  
 Class : 3  
 Sub risk : -  
 Packing group : II

**15. Regulatory information**

Ensure this material in compliance with federal requirements and ensure conformity to local regulations.

**16. Other information****References**

Solvents Handbook, T. Asahara et al, Kodansha Scientific Ltd. (1976)  
 Handbook of dangerous and hazardous chemicals, Japan Industrial Safety & Health Association. (2000-2001)  
 Dangerous Properties of Industrial Materials, 6th ed, N. I. Sax Van Nostrand Reinhold Company (1984)  
 Handbook of Dangerous Substances Springer-Verlag Tokyo (1991)  
 Handbook of 15509 Chemical Products, The Chemical Daily Co. (2009)

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